

Analysis of Thrombi Retrieved From Cerebral Arteries of Patients With Acute Ischemic Stroke

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Background and Purpose—Information regarding the histological structure of thromboemboli that cause acute stroke provides insight into pathogenesis and clinical management.

Methods—This report describes the histological analysis of thromboemboli retrieved by endovascular mechanical extraction from the middle cerebral artery (MCA) and intracranial carotid artery (ICA) of 25 patients with acute ischemic stroke.

Results—The large majority (75%) of thromboemboli shared architectural features of random fibrin:platelet deposits interspersed with linear collections of nucleated cells (monocytes and neutrophils) and confined erythrocyte-rich regions. This histology was prevalent with both cardioembolic and atherosclerotic sources of embolism. “Red” clots composed uniquely of erythrocytes were uncommon and observed only with incomplete extractions, and cholesterol crystals were notably absent. The histology of thromboemboli that could not be retrieved from 29 concurrent patients may be different. No thrombus >3 mm wide caused stroke limited to the MCA, and no thrombus >5 mm wide was removed from the ICA. A mycotic embolus was successfully removed in 1 case, and a small atheroma and attached intima were removed without clinical consequence from another.

Conclusions—Thromboemboli retrieved from the MCA or intracranial ICA of patients with acute ischemic stroke have similar histological components, whether derived from cardiac or arterial sources. Embolus size determines ultimate destination, those >5 mm wide likely bypassing the cerebral vessels entirely. The fibrin:platelet pattern that dominates thromboembolic structure provides a foundation for both antiplatelet and anticoagulant treatment strategies in stroke prevention. (*Stroke*. 2006;37:2086-2093.)

Key Words: cerebral arteries ■ thrombi

Pre-cerebral or cerebral artery occlusions account for 70% to 80% of acute strokes,^{1,2} for which reperfusion therapy is the most efficacious treatment, the occlusive vascular lesion being the target.³⁻⁵ Thromboembolic arterial occlusions may originate from various proximal sources, including venous “paradoxical” sites, mural cardiac thrombi, or atherosclerotic lesions within or proximal to the affected vessel. Given the diverse sources of cerebral thromboemboli, development of new reperfusion treatment strategies would be greatly facilitated by knowledge of the composition of stroke-causing cerebral thrombi in human patients.⁶ Until recently, however, acute cerebral thrombi in humans were inaccessible.

The development of endovascular mechanical embolectomy devices affords a unique opportunity to characterize fresh pathological thrombi in acute ischemic stroke patients. The Merci Retriever System (Concentric Medical, Mountain View, Calif) has been the most widely studied device designed to remove

thrombi from patients experiencing acute cerebral ischemia.⁷⁻⁹ Other mechanical retrieval devices have been used as well,¹⁰⁻¹⁷ but there has been only limited analysis of a few cases and no systematic examination of these unique pathological specimens.

For this report, we analyzed the histology of the first 25 thrombi retrieved from the cerebral circulation of patients treated with the Merci Retriever System and correlated these findings with clinical data, especially those relative to the likely etiology of the thrombotic stroke. The results suggest that the recovered thrombi contain similar structural components, constituted into unique histological entities, and provide insight into the process of thrombus initiation and growth.

Methods

Study Design and Population

This was a histopathological study of the first 25 consecutive thromboemboli retrieved from a cerebral artery from patients with

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acute ischemic stroke at UCLA Medical Center with use of a mechanical embolectomy device (Merci Retrieval System, Concentric Medical, Inc). The study was approved by the UCLA institutional review board; subjects provided written, informed consent; and all procedures were in accordance with institutional guidelines.

Of the 25 patients, 12 were enrolled in the multicenter Mechanical Embolus Removal in Cerebral Ischemia (MERCi) Trial^{7,8} and 3 in the single-center Concentric Retriever Device in Acute Ischemic Stroke (CRD) Study. Nine patients underwent clot retrieval under “off-label” use of the device,¹⁸ based on the attending physician’s case-based judgment that use of the device “for an indication not in the approved labeling” provided the best chance for a good outcome. One patient received “on-label” treatment with the device according to US Food and Drug Administration clearance of the Merci Retriever for this indication. Detailed inclusion criteria for embolectomy included acute occlusion of a proximal, large, intracranial artery; disabling neurological deficit; and initiation of therapy within 8 hours of onset or beyond 8 hours when imaging demonstrated substantial residual penumbral tissue at risk. Key exclusion criteria were the presence of severe extracranial carotid stenosis or suspected intracranial atherosclerosis with superimposed *in situ* thrombus that would obstruct retrieval of a captured intracranial thrombus.

Thrombi were retrieved from the intracranial internal carotid artery (ICA), the middle cerebral artery (MCA), the anterior cerebral artery (ACA), and the vertebral and basilar arteries. Occlusions that occurred in the ICA in combination with the MCA or ACA were categorized as ICA occlusions, whereas MCA occlusions without ICA involvement were categorized as MCA. MCA occlusions were further classified as M1 or M2 according to the involved arterial segment. Occlusions limited to the ACA alone were not observed. The presumed mechanism of an ischemic stroke was determined with use of the modified TOAST stroke subtype algorithm, completed by 2 senior neurologists (S. Starkman and J.L.S.).¹⁹

Embolectomy Procedure

Before removal of the thrombus responsible for the ischemic stroke, all patients underwent conventional 4-vessel cerebral angiography. The embolectomy procedure was performed as described elsewhere.⁸ In brief, loops of the helical nitinol coil retriever device were deployed to capture the thrombus, after which the coil and thrombus were withdrawn into the delivery catheter. The procedure was stopped if recanalization was achieved or if the treatable vessel was not opened after 6 device passes. Vascular reperfusion was based on the Thrombolysis in Myocardial Infarction (TIMI) scale modified for the cerebral circulation,^{8,20} with assignments of 3 (complete antero-grade reperfusion), 2 (partial reperfusion), 1 (reduction in thrombus without reperfusion), and 0 (no reduction in thrombus). Schematic representation of the pre retrieval and postretrieval angiograms of the target vessels was based on angiographic visualizations.²¹ The proximal face of a thrombus was directly visible on antero-grade injections; the distal end either was judged by direct visualization or was estimated by the pattern attained by collateral flow when stagnation or washout precluded direct visualization.

Processing of Thrombi

Thrombus material was fixed in 10% phosphate buffered formalin/2.5% glutaraldehyde. Formalin-fixed specimens were embedded in paraffin, cut at 8- μ m thickness, and stained with hematoxylin and eosin. Thrombus No. 23 also was stained with Gomori methenamine silver for fungus. Histological sections were photographed with an Olympus BX41 microscope with an attached MicroFire digital camera (model S99809). Histological examination was performed without knowledge of the clinical findings and was based on feature detection analysis of functionally distinct processes, including platelet:fibrin accumulations (thrombosis in flowing blood), linear neutrophil and monocyte deposits (surface adherence interactions), and erythrocyte-rich accumulations (whole-blood coagulation).

Results

From May 2001 to March 2005, thrombi were retrieved from cerebral arteries of 25 patients with acute ischemic stroke

(Table 1). There were 16 men and 9 women; the mean \pm SD age was 56.9 \pm 22.0 years, (range, 14 to 90). Mean delay from the defined onset of stroke symptoms until thrombus retrieval was 6.2 \pm 3.1 hours. Presumed etiology was cardioembolic in 16 patients, large-vessel atherothromboembolic with artery-artery embolism in 4, arterial dissection or procedural complication in 3, and cryptogenic in 2.

There was involvement of the right and left anterior circulation in 9 and 15 patients, respectively, and of the basilar artery in 1 patient (Figure 1). Full recanalization of the artery (TIMI 3) was established in 8 of 25 patients (32%), partial recanalization (TIMI 2) in 14 (56%), and perfusion past the initial obstruction without distal branch filling (TIMI 1) in 3 (12%). Four thrombi (Nos. 20 through 23) were retrieved from patients who underwent prior intravenous tissue plasminogen activator treatment, with full patency achieved in 3 patients. The interval from stroke onset to thrombus retrieval did not differ among patients with TIMI 3 (5.3 \pm 1.9 hours), TIMI 2 (7.6 \pm 4.0 hours), and TIMI 1 (5.0 \pm 1.0 hours; 1-way ANOVA, $P=0.22$) recanalization. The site of vascular occlusion was not correlated with vessel recanalization, with TIMI 3 achieved in 4 of 12 (33%) ICA occlusions versus 5 of 12 (42%) MCA occlusions.

Extracted thrombi were often retrieved as a single mass (9/25, 36%), but most were retrieved in multiple fragments. The mean size of extracted thrombus was 6.6 \pm 7.8 mm (length) by 2.4 \pm 1.2 mm (width). There was a significant difference in thrombus size for the 12 ICA thrombi compared with the 12 obtained from the MCA only (width, 2.8 \pm 1.2 versus 1.8 \pm 0.8 mm, $P=0.033$; length, 10.1 \pm 10.2 versus 3.1 \pm 1.5 mm, $P=0.033$; $P=0.027$). Maximum width of MCA thrombi was 3 mm, compared with 5 mm for ICA thrombi (Figure 2).

Histological examination (Figure 3) showed that no 2 thromboemboli were similar in overall appearance, each demonstrating a distinctive pattern, with layers or “serpentine” fibrin:platelet bands interspersed with accumulations of nucleated cells and erythrocyte-rich accumulations. At higher magnification, the serpentine pattern (No. 7) of convoluted bands of fibrin:platelets reflected contiguous linear deposits of nucleated cells (not shown). Figure 4 (top) shows red clots within 2 thromboemboli: sample No. 21, which is folded back over a clot, and sample No. 1, with a fibrin-rich distal portion and an erythrocyte-rich zone on the proximal tail. Simple red clots (No. 15, bottom right) were recovered from only 3 patients, each having had incomplete vascular reperfusion. Calcific deposits and cholesterol crystals were not seen in extracted material.

Correlation of thrombus histology with presumed etiology, vessel location, and target-vessel response (Table 2) showed no prevalence of histological structure with cardioembolic or arteriopathic etiology, no relation with ICA or MCA occlusion, and no predictive attribute for successful extraction. In addition to the 25 patients from whom thrombus was extracted during the study time period, an additional 29 patients underwent endovascular clot retrieval without successful thrombus extraction. Among these patients, there was minimal recanalization in 13 (45%), partial recanalization in 14 (48%), and complete recanalization in 2 (7%). Patients in whom clot extraction was achieved differed from patients without successful clot extraction in age (57 versus 69 years, $P=0.026$) but not in sex, time to

TABLE 1. Patient Characteristics: Chronological Observations

No.	Sex	Age, y	Presumed Etiology	Vascular Site	Onset to Retrieval, h	Thrombus Histology
1	M	62	Atrial fibrillation	Left ICA	6	Fibrin enriched
2	F	73	Atrial fibrillation	Right ICA, M1, A1	6	Fibrin enriched
3	M	64	Cerebral angiography	Left M1-2	7	Fibrin enriched
4	M	44	Arterial dissection	Left ICA, M1	8	Serpentine
5	F	28	Aortocarotid artery surgery for Takayasu arteritis	Left M1-2	12	Erythrocytic
6	M	59	Atrial fibrillation	Right ICA, M1-2, A1	7	Layered
7	M	86	Atrial fibrillation	Right A1, M1	6	Serpentine
8	M	32	Cryptogenic	Basilar, right P1	18	Serpentine
9	M	53	Atrial flutter	Left ICA, M1, A1	3	Layered
10	M	85	Left ventricle thrombus	Right ICA, M1, A1	4	Layered
11	F	36	Rheumatic mitral stenosis	Left M1-2	6	Layered
12	F	90	Atrial fibrillation	Left M2	6	Serpentine
13	M	58	Artery-artery embolism from extracranial (ICA) atherosclerotic source	Right ICA, M2	10	Serpentine
14	M	75	Atrial fibrillation	Right M1-2	8	Layered
15	F	58	Post-cardiac transplant left ventricle thrombus	Left M1	4	Erythrocytic
16	F	30	Patent foramen ovale	Left M1	6	Serpentine
17	M	48	Artery-artery embolism from extracranial (aorta) atherosclerotic source	Left ICA, M1	4	Serpentine
18	M	73	Artery-artery embolism from extracranial (ICA) atherosclerotic source	Left M1	4	Layered
19	F	72	Atrial fibrillation	Right ICA, M1	5.5	Erythrocytic
20	M	39	Atrial fibrillation	Left M1	5	Serpentine
21	M	83	Cardiac arrhythmias	Left ICA, M1	7	Serpentine
22	F	32	Artery-artery embolism from extracranial (ICA) atherosclerotic source	Right M1	7	Layered
23	M	14	Mycotic aortic valve endocarditis	Right M1	2	Mycotic
24	F	87	Atrial fibrillation	Left ICA, A1, M1-2	3	Layered
25	M	40	Cryptogenic	Left M1	7	Vessel intima

start of the retrieval procedure, TOAST stroke subtype, or site of target occlusion.

Subject No. 23 had mycotic aortic endocarditis with embolic occlusion of the right M1 and M2 segments of the MCA, underwent retrieval within 2 hours of symptom onset, and had an excellent clinical recovery, coincident with full revascularization. Sample No. 25 showed a small atheroma with attached arterial intima and subintima, due to inadvertent extraction of an unrecognized in situ atherosclerotic lesion. Despite the denuded surface, the patient had an excellent clinical and vascular response without recurrence of symptoms.

Discussion

This is the first systematic histological analysis of thromboemboli removed from the cerebral artery network of patients with acute ischemic stroke. Our observations on stroke-causing thromboemboli obtained (on average) 6 hours after symptom onset extend the clinicopathological observations of Torvik and Jørgensen made almost 50 years ago²² on post-mortem material, for which “recent” occlusion was defined as <1.5 months old.

Each of our samples had a distinctive overall histological appearance (Figures 3 and 4), such that no 2 were even remotely identical. Yet the component parts of most cerebral thromboemboli were remarkably similar, 75% showing a complex pattern of lightly stained platelet:fibrin areas, interspersed with linear or broad deposits of nucleated cells, often with intervening collections of erythrocytes. “Red” clots that contained a mass of erythrocytes with evenly dispersed nucleated cells were either enclosed within thromboemboli or extracted intact from 3 subjects (of 25) who had incomplete vascular recanalization. We interpret these findings to indicate that the “red” clots reflect postocclusion clot formation in a distal static column of blood, rather than clotting at the proximal arterial or cardiac source of the embolus. Calcific emboli have been noted on computed tomography scans of patients with stroke,²³ but calcific components in retrieved thromboemboli were notably absent in this series, suggesting that embolization of calcific valvular or plaque contents is not a common pathogenetic process for acute ischemic stroke due to a large intracranial arterial occlusion.

The extraordinary diversity of histological pattern, despite the presence of common component parts of fibrin, platelets, nucle-

#	ANGIOGRAM		TARGET VESSEL RESPONSE	THROMBUS (mm) (LENGTH X WIDTH)	#	ANGIOGRAM		TARGET VESSEL RESPONSE	THROMBUS (mm) (LENGTH X WIDTH)
	PRE-RETRIEVAL	POST-RETRIEVAL				PRE-RETRIEVAL	POST-RETRIEVAL		
1			3	6 x 5	14			2	2 x 2
2			2	3 x 3	15			1	2 x 1
3			2	2 x 1	16			3	4 x 3
4			2	31 x 3	17			2	2 x 1
5			2	1 x 1	18			3	5 x 2
6			2	6 x 3	19			2	3 x 3
7			3	10 x 4	20			1*	4 x 2
8			2	7 x 2	21			3*	6 x 4
9			3	6 x 5	22			3*	4 x 3
10			2	15 x 2.5	23			3*	2 x 1
11			2	2 x 2	24			2	3 x 2
12			1	3 x 1	25			3	6 x 2
13			2	30 x 2					

Figure 1. Schematic representation of pre retrieval and postretrieval angiograms. Asterisk denotes thrombus retrieved from patients after prior intravenous thrombolytic therapy with tissue plasminogen activator.

ated cells and “red” clot,²⁴ reflects the random, almost chaotic, conditions of blood flow, shear, and turbulence at sites of thrombus initiation and growth. The complex histological patterns occurred in thromboemboli retrieved from patients with both cardioembolic and arteriopathic etiology (Table 2), so it is likely that such local conditions are present on fresh arterial lesions and mature intracardiac thrombi and that such thrombi develop from the start under similar pathological influences. In contrast to traditional teaching²⁵ that emphasizes differences between “red” clots forming at sites of cardiac origin due to stagnant flow and “white” clots forming at sites of arterial origin due to high flow, our findings suggest an underlying common-

ality of histological component structure of thromboemboli from both cardiac and arterial sources.

Thromboemboli with complex histology were equally likely to occlude the larger ICA as the smaller MCA recipient arteries. Only emboli <3 mm wide reached the MCA, whereas larger emboli, stretching up to 30 mm in length but no more than 5 mm in width, obstructed the ICA (Figure 2). The vertebral-basilar artery was occluded in only 1 of our 25 cases, but relatively large thrombi have been removed from this vessel.^{15,26} This observation suggests that large emboli should not cause an intracranial ICA or MCA ischemic stroke, simply because a width in excess of 5 mm precludes penetration into the distal ICA. Such emboli

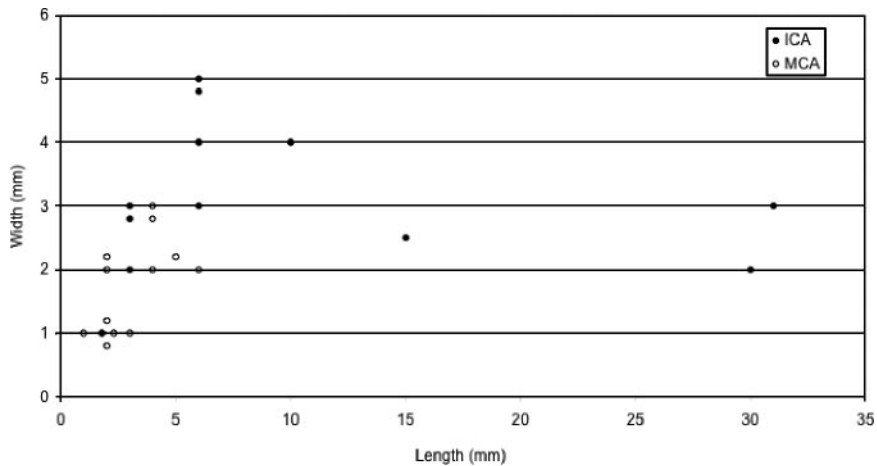


Figure 2. Dimensions of retrieved thrombi. Open circles refer to thrombi obtained from the ICA, and closed circles show thrombi from occlusions limited to the MCA.

are likely to bypass the cerebral circulation altogether and cause ischemic occlusion of larger-diameter arteries, such as in the lower extremities.²⁷

Vascular response (TIMI score) correlations provided useful insights into pathogenesis. First, there was no correlation with histology (Table 2), suggesting that all emboli contain similar structural components that contribute to “purchase” of the extraction device into the embolus. Second, the delay between

symptom onset and procedure initiation did not influence vascular response, suggesting that the embolus is compressed quickly after impaction into a cerebral artery. Last, complete mechanical extraction of thrombus was equally successful from the ICA or the MCA, reflecting simple access of the catheter to the thromboembolus. This differs from results with thrombolytic therapy, for which greater efficacy is noted for smaller MCA occlusions than for larger ICA occlusions.²⁸ Because histology

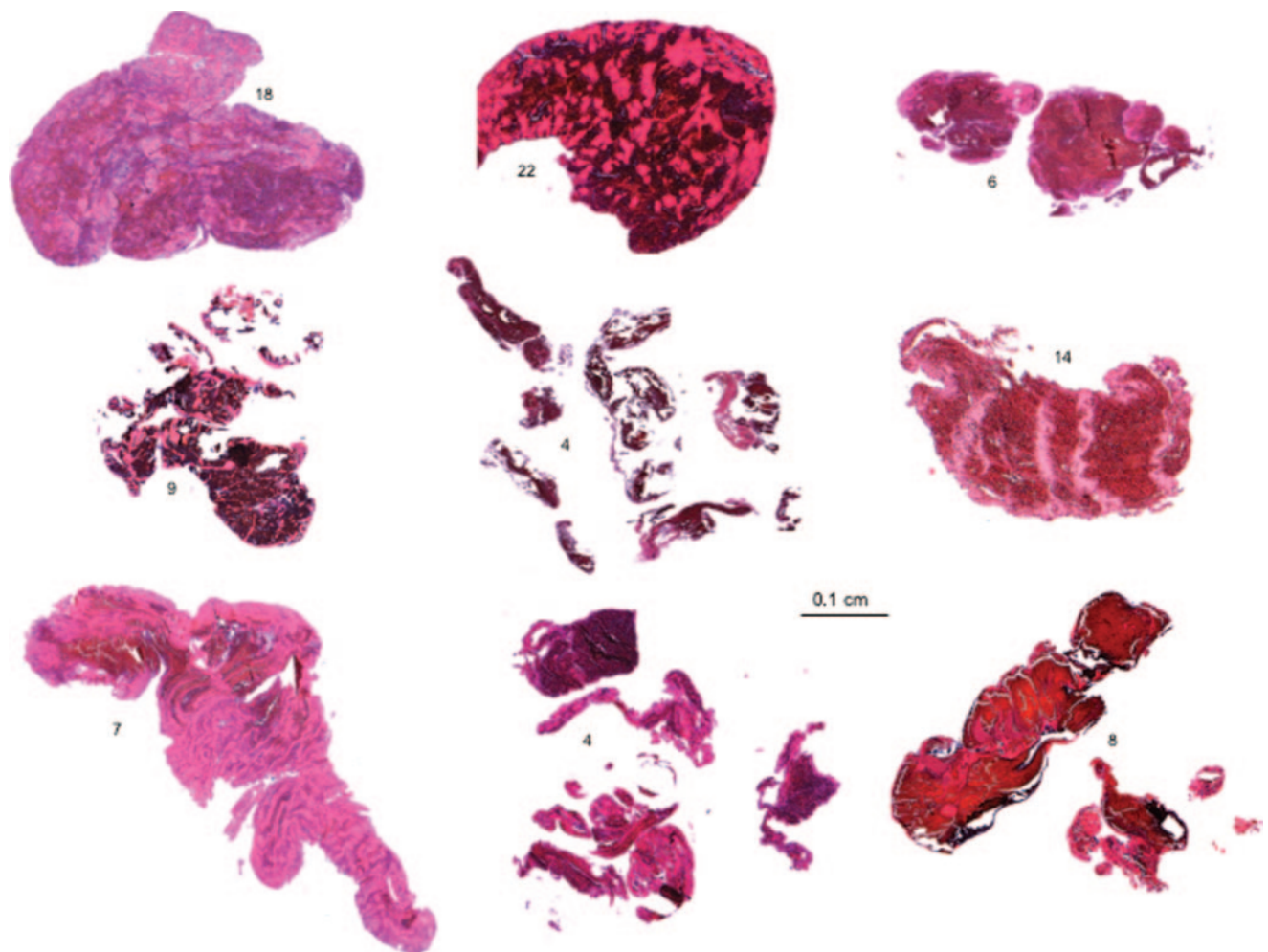


Figure 3. Hematoxylin and eosin-stained sections of 9 thrombi.

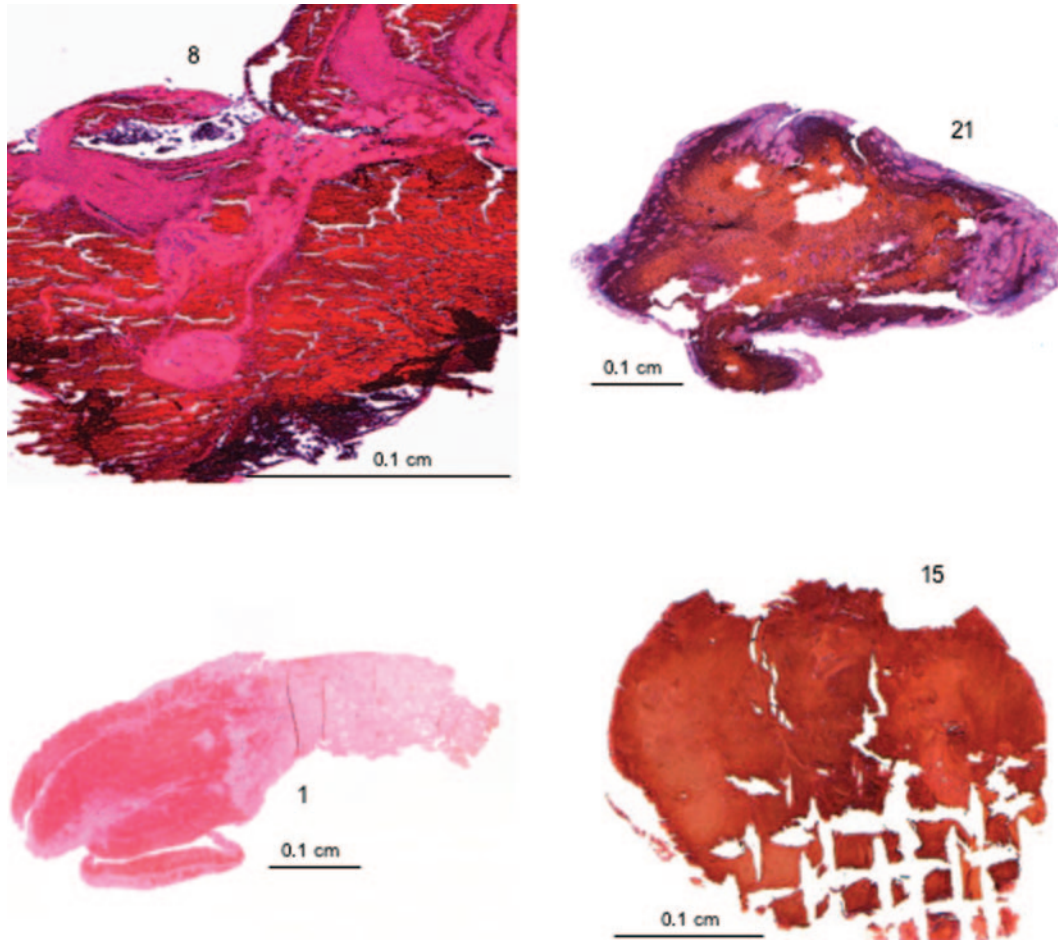


Figure 4. Thrombi with entrapped collections of blood clot (top left and bottom left), compared with an erythrocyte-predominant clot, presumably formed in a static area after embolic impaction (bottom right). Hematoxylin and eosin–stained sections.

does not differ between MCA and ICA thromboemboli, successful thrombolytic therapy depends more on the volume of thrombus to be dissolved than on its structure.

Several circumstances deserve special mention. First, 4 patients received tissue plasminogen activator before they under-

went mechanical extraction, with 3 achieving full recanalization (Figure 1). Whether pretreatment with tissue plasminogen activator “conditioned” the thrombi for easier device extraction merits further evaluation, but the effect cannot be attributed to a distinct histological pattern. Second, an in situ fungal cerebral

TABLE 2. Retrieved Thrombus Histology Relative to Vascular Origin and Outcome

	Complex Structure					Total
	Layered	Serpentine	Fibrin Enriched	Erythrocytic	Other	
No. of cases	8	9	3	3	2	25
Presumed etiology						
Cardioembolic	6	5	2	2	1	16
Atherosclerotic or nonatherosclerotic arteriopathy	2	3	1	1	0	7
Cryptogenic	0	1	0	0	1	2
Occluded artery						
ICA	4	5	2	1	0	12
MCA	4	3	1	2	2	12
Basilar	0	1	0	0	0	1
Target-vessel TIMI response						
1	0	2	0	1	0	3
2	5	4	2	2	0	13
3	3	3	1	0	2	9

embolus has been documented for the first time and has been demonstrated to be responsive to mechanical embolectomy. Third, an atherosclerotic plaque and adjoining vascular intima were sheared from the vessel wall of 1 subject on withdrawal of the catheter, indicating that the retriever is best used for emboli to normal recipient arteries and that occlusions overlying in situ atherosclerotic plaque are likely better treated with other nonretrieval techniques.

For prevention therapy, our observations provide an explanation for large-scale clinical trial findings that both antiplatelet and anticoagulant agents are beneficial for averting cerebral thromboemboli of both cardiac and arterial origin. The predominance of fibrin:platelets in 6 of 7 (86%) of arterial-source cerebral thromboemboli (Table 2) accords with findings demonstrating that aspirin and warfarin are about equally effective in stroke prevention in patients with ischemic stroke of arterial origin.^{29,30} Similarly, the composition of thromboemboli in patients with atrial fibrillation is consonant, with results showing that aspirin is effective in reducing atrial fibrillation-related stroke, albeit not as effectively as warfarin.^{31,32}

Our conclusions are limited by sampling constraints. The data tell us only about cases in which thrombi could be retrieved, but those that remain in place or occlusive material that is fragmented without extraction may differ from retrieved thromboemboli, and extracted particles may not represent the entire in situ thrombus. The cohort consists of patients with large intracranial vessel occlusions and does not include patients with distal, superficial branch occlusion, deep penetrator occlusion, or thrombus forming in situ on intracranial atherosclerotic lesions. The younger age of patients from whom thrombus was extracted may indicate the greater clot friability and/or greater vessel tortuosity in older patients, which make full retrieval of target occlusions more difficult. Patients with suspected intracranial atherosclerotic lesions with in situ supervening thrombosis were excluded from retriever therapy. Likely because the retriever device was too large to navigate beyond the M2 segment of the MCA, we did not observe cholesterol crystals, which have been noted in more distal vessels such as the leptomeningeal arteries or terminal cortical branches.³³

In summary, we present results on the histology and size of the first 25 cerebral artery thrombi extracted from patients with acute ischemic stroke with a mechanical device. The large number of cases allows for fresh insights into the pathogenesis and therapy of large vessel ischemic stroke.

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Disclosures

J.L.S. served on a scientific advisory board on secondary prevention to Boehringer Ingelheim, and serves on a Speaker's Bureau on secondary prevention of Boehringer Ingelheim. S.S. served on a scientific advisory board to Genentech. G.D. serves on a scientific advisory board and owns stock in Concentric Medical. The University of California is a copatent holder for the Merci Retriever.

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